Sex ratio of multiple sclerosis in Canada: a longitudinal study

*Sarah-Michelle Orton, Blanca M Herrera, Irene M Yee, William Valdar, Sreeram V Ramagopalan, A Dessa Sadovnick, George C Ebers, for the Canadian Collaborative Study Group**

Lancet Neurol 2006; 5: 932–36

Published Online October 4, 2006
DOI:10.1016/S1474-4422(06)70581-6

*Members listed at end of report

Wellcome Trust Centre for Human Genetics and Department of Clinical Neurology, University of Oxford, Oxford, UK (S-M Orton BSc, B M Herrera BSc, W Valdar PhD, G C Ebers MD, S V Ramagopalan BA)**; and Department of Medical Genetics and Faculty of Medicine, Division of Neurology, University of British Columbia, Vancouver, Canada** (I M Yee MSc, A D Sadovnick PhD)

Correspondence to: Prof George Ebers, Department of Clinical Neurology, Radcliffe Infirmary, University of Oxford, Oxford OX2 6HE, UK
george.ebers@clneuro.oxford.ac.uk

Summary

Background **Incidence of multiple sclerosis is thought to be increasing, but this notion has been difficult to substantiate. In a longitudinal population-based dataset of patients with multiple sclerosis obtained over more than three decades, we did not show a difference in time to diagnosis by sex. We reasoned that if a sex-specific change in incidence was occurring, the female to male sex ratio would serve as a surrogate of incidence change.**

Methods **Since environmental risk factors seem to act early in life, we calculated sex ratios by birth year in 27 074 Canadian patients with multiple sclerosis identified as part of a longitudinal population-based dataset.**

Findings **The female to male sex ratio by year of birth has been increasing for at least 50 years and now exceeds 3·2:1 in Canada. Year of birth was a significant predictor for sex ratio ($p<0·0001$, $\chi^2=124·4$; rank correlation $r=0·84$).**

Interpretation **The substantial increase in the female to male sex ratio in Canada seems to result from a disproportional increase in incidence of multiple sclerosis in women. This rapid change must have environmental origins even if it is associated with a gene–environment interaction, and implies that a large proportion of multiple sclerosis cases may be preventable in situ. Although the reasons why incidence of the disease is increasing are unknown, there are major implications for health-care provision because lifetime costs of multiple sclerosis exceed £1 million per case in the UK.**

Introduction

There is a consensus in many countries that the incidence and prevalence of multiple sclerosis has been increasing. However, this change is often attributed to inconsistencies in ascertainment and epidemiological methods. Restudy of populations often identifies additional cases that were missed during the first study. Differing views have been difficult to resolve because occurrence of several simultaneous changes that affect perception of incidence have had potential to confound the results.

Prevalence and incidence of multiple sclerosis have varied in reported studies and are related, at least in part, to the geography of the disease.[1,2] Although there seems to be a general trend over the years towards increased incidence and prevalence, results in different countries have not been easy to compare; some regions have reported increased incidence,[3–12] whereas others have shown no change or decreased incidence.[13,14] Ascertainment and study design undoubtedly confound multiregion comparisons as well as differential increases in survival rates for prevalence. Ways of overcoming or reducing ascertainment bias include uniformly sampling the same population over time or establishing changes with an internal variable in the same study group. Showing that changes have taken place in a subset of patients enables use of an internal contemporaneous matched control group, and a candidate for such a subset is the measurement of sex ratio.

Studies from several countries, including the USA,[10] Australia,[9] and Japan,[15] have shown the female to male sex ratio of multiple sclerosis cases to increase over time when serial cross-sectional comparisons were made. We have shown that the rate of disease has been increasing in Canada. A heightened risk for later born female children was seen in very large pedigrees with sibships often spanning two decades or more in birth timing.[16] Several lines of evidence, especially migration studies,[17–21] have pointed toward determination of risk for the disease in early life. With the clear recognition that environmental factors in the disease act at a broad population level we have been studying the timing of this effect in Canada, albeit through approaches that are necessarily indirect. A month-of-birth effect with a May peak and a November nadir in risk,[22] a maternal parent-of-origin effect in half-siblings,[23] and the finding of an excess concordance and age of onset correlation for dizygotic twins compared with siblings (Ebers G, Sadovnick A, unpublished) imply that gestational timing might be a factor.

With these considerations in mind, we sought to assess whether the female to male ratio of patients with multiple sclerosis in Canada has changed over the years in a population-based sample stratified by year of birth.

Methods

Study population

The Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis (CCPGSMS)[24] has been gathering detailed information about demographics, family history, and clinical aspects of disease for patients with multiple sclerosis attending any of the participating Canadian multiple sclerosis clinics. Details on the study design and diagnostic criteria have been published before.[24]

The initial cohort of 29 478 observed patients with multiple sclerosis comprised 21 054 women and 8424 men, with birth years spanning from 1891 to 1993. The

mean numbers of women and men by year of birth were averaged over 5-year blocks to calculate the sex ratio and corresponding CIs. Each 5-year period from 1931 to 1980 contained a minimum of 500 identified cases, comprising 27 074 participants incorporated into the statistical analysis. The number of participants born before 1931 and after 1980 was comparatively small and those born before 1931 might have required increasing corrections to account for differences in longevity in men and women. Patients born after 1980 represent a cohort with a relatively early age of onset as they have only just reached the peak age of onset of the disease[25] and thus might not accurately estimate the ratio of this birth-year cohort.

Statistical analysis

To test the significance of birth year as a predictor of sex ratio in multiple sclerosis we used binomial logistic regression, modelling the true proportion P_y of women with multiple sclerosis born in each year (y) as $\ln [P_y/(1- P_y)]=\beta_{intercept}+ \beta_{YOB}y$, such that the sex ratio increases by a factor of $e^{\beta YOB}$ per year and the observed number of female patients N_{Fy} is distributed as N_{Fy}~Binomial $(P_y, N_{Fy}+ N_{My})$, where N_{My} is the corresponding number of men with the disease. The likelihood ratio test was used to assess whether β_{YOB} was significantly different from zero. All logistic models were analysed in the statistical package R.[26] The analyses were repeated with the exclusion of patients born outside Canada (n=2156), most of which were from northern Europe.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

Of the 27 074 cases included in the analysis (born 1931–80), 19 417 were women and 7657 were men, with a mean of 480 cases per year of birth and 2400 cases per 5-year block (table). The sex ratio for the entire cohort (1891–1993, n=29 875) ranged from 1·33 to 3·96 and this range was slightly less (1·90–3·21) when the data were reduced to 5-year blocks. Comparison of the sex ratio of multiple sclerosis patients by birth year showed a significant, progressive, gradual increase, with an apparent hiatus in the early 1970s (figure).

Statistical analysis using logistic regression showed that year of birth is a significant predictor for sex ratio ($p<0·0001$, $\chi^2=124·4$, $\beta_{YOB}=0·014$; Spearman's rank correlation $r=0·84$). Individual year-of-birth data, as opposed to 5-year blocks, were used in the logistic regression. The model showed that with each year the ratio of women to men increased by a factor of 1·014 ($e^{\beta YOB}$), which corresponds to a percentage increase in women of 0·85% per year over the period 1931–80. The variation in year-to-year sex ratio, which could be substantial, did not in any year fall outside the 95% CIs for this determination (data not shown).

	Number of cases per 5-year block		Sex ratio	
			Per year of birth	Per 5-year block*
Mean	2400	Mean	2·54	2·51
Mean women	1716	Minimum	1·68 (1932)	1·90 (1931–35)
Mean men	684	Maximum	3·96 (1977)	3·21 (1976–80)

*Data averaged over 5-year blocks, from 1931 to 1980.

Table: **Sex ratio in the Canadian multiple sclerosis cohort from 1931 to 1980 (n=27 074)**

The analysis was repeated in non-Canadian born patients (n=2156) and the increasing trend paralleled the results for the entire cohort, although the mean female to male ratio was lower (2·16) and more variable in this smaller sample subset, which included those from low-risk areas.

Discussion

Our findings show that the female to male sex ratio of multiple sclerosis has been increasing in Canada for at least 50 years. Cross-sectional studies within selected

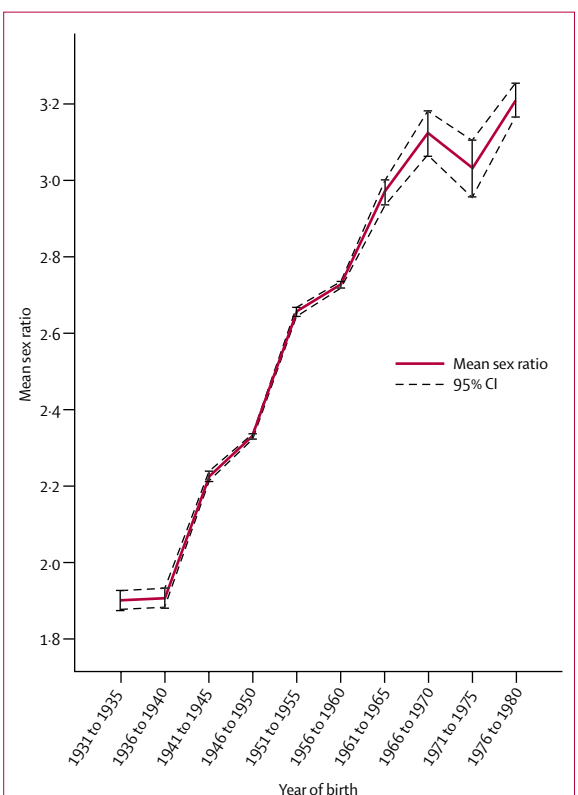

Figure: **Female to male ratio of multiple sclerosis patients from the CCPGSMS by year of birth, spanning a 50 year period (n=27 074)**
Spearman rank correlation, r=0·84. Logistic regression analysis showed the increasing trend was significant (p<0·0001).

sites in Canada are uniformly in agreement with this interpretation. These findings accord with the widespread perception that incidence and prevalence of multiple sclerosis have generally increased. Although our data do not shed light on the reasons for these changes, they do bear on the plausibility of some proposed factors. Several lines of observational evidence across Canada belie the possibility that the incidence of multiple sclerosis by birth year has not really changed and that the sex-ratio findings are the result of a compensatory decrease in incidence among men. Serial sampling has shown an overall increase with no reduction in incidence among men[27,28] and recent comparison of two cross-sectional studies in Newfoundland[29] documented a selective increase in rates of affected women.

Differences in time to diagnosis and age of onset could potentially affect the sex ratio in the short term if a relative delay was sex specific. Even if such a delay were more prolonged—ie, 10 years—it would only affect the most recent quinquennial results; more seriously affected individuals would eventually be ascertained and the contribution to their birth year cohort would still be registered. Hence, any short-term fluctuations caused by putative sex-specific delays in diagnosis should be serially washed out because of the length of the observations and the use of a year-of-birth analytical approach. Furthermore, although women do have a slightly earlier onset than men (mean difference of 1 year[25]), their time from clinical onset to diagnosis in Canada is identical (mean of 3 years in each group). The extent of the change in sex ratio, its progressive nature, and use of year of birth as the predicting variable make it unlikely that the findings could be explained by any artefact related to ascertainment.

The sex ratio in multiple sclerosis in the early 1900s was reported by several observers to be close to unity.[30] This notion has been dismissed as resulting from greater ascertainment of bread-winning men early in the past century. From 1870 to 1910, opinions differed as to whether multiple sclerosis was more prominent in men or in women or if they were equally affected.[31] Most reports were anecdotal, but a case series reviewing nearly 2000 patients' records from the early 1900s showed that men were more affected than women in the ratio of three to two.[32] Consensus wavered over the next 20 years, but favoured a ratio close to unity. By the 1940s, it was no longer believed that men were more commonly affected than women[31,33–35] and the US National MS Society declared that the disease affected men and women equally.[36]

Multiple sclerosis was not viewed to be more common in women until the 1950s and 60s[37,38] and a review of 14 prevalence surveys undertaken before 1977 concluded that the female to male ratio was 1·4:1.[39] Evidence lending support to a female preponderance continued into the last two decades of the 20th century with a consensus that women were about twice as likely to develop the disease than were men.[40,41] However, this 2:1 ratio continues to be challenged and there is much evidence to suggest that the difference is significantly higher in some regions.[2,42] Despite this history, little significance has been attached to the meaning of sex-ratio variation in a monograph on multiple sclerosis.[1]

Our analysis is not without potential confounders, although some of these would serve to decrease not increase the sex ratio over time. The premature mortality of men compared with women serves to inflate the observed sex ratios, and correction for this factor would enhance the slope of the graph in the figure. We observed no discernible effect on the increasing ratio related to the wartime years in which many young Canadian men died, nor from the small increase in male births post-war, although the effects were not analysed in detail.

Additionally, a modest tendency of sex ratio to decrease with rising age of onset and diagnosis has been reported (unpublished). This would result in the vanguard of a year-of-birth cohort having a higher sex ratio than the full cohort. However, given that more than 90% of multiple sclerosis patients have onset before 50 years of age,[43] there can be very few additional cases to birth cohorts before 1955 and the observed increasing trend predates this period. Indeed, the finding of a sex ratio related to age of onset must now be reconsidered in light of the studies reported here. The higher female to male sex ratio in younger onset cases could at least in part be a result of the changing sex ratio over time, rather than a confounder of it. Since there is no indication that multiple sclerosis in men has decreased, it seems that the sex ratio change is determined by a preferential increase in affected women. Logistic regression analysis showed that the trend for increasing year of birth as a predictor of sex ratio was highly significant over the 50-year period analysed ($p<0·0001$, $\chi^2=124·4$, $\beta_{YOB}=0·014$). The female to male ratio has increased progressively from around 1·90 to 3·21 (1931–35 to 1976–80 quinquennia; rank correlation $r=0·84$) and excluded data suggest that the increase began before 1930. An increasing trend consistent with that seen in the entire cohort was observed in the immigrant patients (n=2156), although these results need substantiating in a larger population. Although we suspect the results will be reproducible in northern European populations, we cannot rule out the prospect that the changing sex ratio in the immigrants is affected by later-life events common to both immigrants and native born patients. The large sample size and time frame considered drive the significance of the observed trend and provide compelling support for findings from previous cohort and cross-sectional studies[6,7,9,10,44,45] that report multiple sclerosis incidence and sex ratio are on the rise. The ratio increase is unlikely to be merely a result of changes in diagnostic procedures, improved ascertainment, population heterogeneity, public awareness, or better patient recording practices.

The factors causing the increasing number of women with multiple sclerosis can only be speculated on, but, given the short duration over which this is occurring, genetic change can be excluded. These factors must be

environmental, perhaps resulting from gene–environment interactions. An association of multiple sclerosis with smoking has been shown,[46] and smoking has increased in women over the years, for which we have not corrected. Although the rising sex ratio seems to predate the changes in smoking behaviour of women, some effect cannot be ruled out. Another candidate is the use of oral contraceptives. Although there is convincing evidence that oestrogens strongly affect the sex ratio of spontaneous autoimmunity[47] and their role in multiple sclerosis and other autoimmune diseases has been widely accepted, oral contraceptive use does not increase risk for the disease.[48–50] Furthermore, these ratio changes seem well-established long before ubiquitous oral contraceptive use in the late 1960s, despite the widely perceived role of oestrogens in risk for multiple sclerosis in women.[51] The large concordance ratio between monozygotic female twins and female–female dizygotic twins,[52] a comparison in which oestrogens are controlled, is noteworthy.

The environmental effect causing the shift in sex ratio could be attributed to changes in lifestyle factors of women. These include higher numbers and changing roles of women in the workforce, outdoor activity, dietary habits, and alterations in menarche and in the timing of childbearing years, among others. Many of these possibilities are amenable to case–control studies. For the maternal parent-of-origin effect to be operative,[23] this would have to preferentially target women. Whatever the environmental influence might be, it seems to have long been at a maximum in Sweden,[14] but is changing in Canada and the USA,[7] and probably in other European regions,[44] and is either less common or protected against in certain other regions.[53] The increasing sex ratio then draws attention to countries in which the female to male ratio is intriguingly low.[53–58] If a relative under-representation of women is responsible for lower prevalence in these regions, this would provide important clues to the pathogenesis of the sex difference in risk and therefore to the nature of a major environmental factor in the disease.

Multiple sclerosis poses a significant burden on health-care costs and affects work productive capacity and quality-of-life years of those affected. Health care and research bodies have come under scrutiny recently in order to provide the most up-to-date therapeutic regimens, disease management programmes, and prevention strategies. An accurate understanding of epidemiological characteristics of multiple sclerosis, especially if shown to be increasing, not only provide key insight into possible disease causes and pathogenesis, but also have implications in health-care strategies, public-health recommendations, and focus of research efforts. Interestingly, there is year-to-year variability within the 5-year blocks used to illustrate the data. The significance of this variability is unclear and detailed examination of fluctuations in specific environmental factors on a year-to-year basis could provide insight into sex-specific susceptibility factors.

It has been known for some time that risk for multiple sclerosis is related to geographic place of birth and residence but not whether this risk could be reasonably altered without migrating. These data imply that a large proportion of multiple sclerosis cases can in fact be prevented in situ. They also draw attention to the potential value of using year of birth and sex ratio as parameters for further exploration of these observations. Since the incidence seems to be changing but is difficult to measure, the sex ratio could provide a ready therapeutic target for intervention or prevention studies.

From the standpoint of the effect of multiple sclerosis on health-care economics,[59] the implications of this sustained increase in female cases are staggering. Whether these results extend to other populations should be easy to determine using sex ratio by year of birth as a partial surrogate for incidence. Given that the increasing trend in female to male sex ratio of immigrant patients mirrored that of Canadian-born patients, we predict that this trend will be found worldwide.

Contributors

S-MO participated in the writing of the manuscript, literature searches, data analysis, and production of figures and tables. BMH participated in the writing of the report and did literature searches. IMY compiled the raw data and managed the database. WV did the statistical analyses. SVR contributed to editing, reference searching, and intial set-up. GE and ADS planned and executed the study with their students and colleagues.

Conflicts of interest

We have no conflicts of interest.

Acknowledgments

We thank the members of the Ebers lab, including Katie Morrison, Matthew Lincoln, and Michael Chao. This study was made possible through grants from the MS Society of Canada and its research foundation. S-MO was supported by a Clarendon scholarship (University of Oxford) and BMH was supported by a UK MS Society studentship. SVR was funded by a UK MRC studentship.

Canadian Collaborative Study Group members

Vancouver: J J-F Oger, D W Paty, S A Hashimoto, V Devonshire, J Hooge, J P Smythe, T Traboulsee; *Calgary*: L Metz; *Edmonton*: S Warren; *Saskatoon*: W Hader; *Ottawa*: R Nelson, M Freedman; *Kingston*: D Brunet; *Hamilton*: J Paulseth; *London*: G Rice, M Kremenchutzky; *Toronto*: P O'Connor, T Gray, M Hohol; *Montreal*: P Duquette, Y Lapierre; *Quebec City*: J-P Bouchard; *Halifax*: T J Murray, V Bhan, C Maxner; *St Johns*: W Pryse-Phillips, M Stefanelli

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